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- SYODAI, Hidekazu  
Takatsuki-shi, Osaka 569-11 (JP)
- NAKAJIMA, Chisato  
Osaka-shi, Osaka 558 (JP)

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(71) Applicant: SHIONOGI & CO., LTD.  
Osaka-shi, Osaka-fu 541 (JP)

(74) Representative:  
Baverstock, Michael George Douglas et al  
BOULT WADE TENNANT,  
27 Fumival Street  
London EC4A 1PQ (GB)

(72) Inventors:

- SUZUKI, Yusuke  
Izumi-shi, Osaka 594 (JP)

(54) **GELATIN CAPSULE WITH ADJUSTED WATER ACTIVITY**

(57) A gelatin capsule having adjusted water activity and preserved in a closed system, which contains, packed therein, an additive(s) selected from carboxymethyl cellulose calcium, crosscarmellose sodium, partially gelatinized starch and polyvinyl polypyrrolidone in the proportion of 50 to 150 wt. % of the total quantity of the gelatin of the said capsule.

EP 0 818 195 A1

## Description

The present invention relates to a gelatin capsule having an improved internal moisture stability in a closed system through the adjustment of the water activity of the capsule content.

5 The quality of a capsule, that is, the stability of its structure, the pharmacological activity of contained drugs and its appearance is closely related to the water or moisture activity. For example, it is known that, even if a gelatin capsule was manufactured under appropriate conditions, the moisture in the capsule coating and the contained drugs evaporate during preservation in a closed system, especially under heating, which possibly leads to a hyper humidity condition (hyper water activity) inside the capsule. When a contained drug comprises an active ingredient liable to change with 10 moisture, or when moisture cannot be separated easily from an active ingredient and impurities unstable to moisture co-exist, the contained drug necessarily contacts the free water present inside the capsule and can be de-stabilized with the elapse of time. This would result in not only a change in the appearance such as coloration but also a decrease in the activity of an active ingredient. In addition, the gelatin capsule itself may become insoluble and soft, which may be followed for example by deformation. In general, the adjustment of water activity, especially its reduction, has previously been carried out by placing a drying agent such as silica gel into the container for packaging capsules so as to 15 reduce the internal moisture of the capsules. However, it is not easy to adjust the water content in the capsule coating appropriately by this method. Especially, in the case of gelatin capsules, too much reduction in the water content may cause cracks or crack breakages, leading to damage or deformation of capsules. The normal water content or moisture content of a gelatin capsule coating is between 12 and 16% and, when it is reduced below 10%, in particular, below 7 - 8%, cracks may be caused by only slight impact. Therefore, it is desirable to decrease the content of free water inside 20 a capsule while maintaining adequately the water content in the gelatin coating. However, the manufacture of such capsules has been difficult.

There have been reported stabilized gelatin capsules, for example, in Japanese Patent Publication (KOKAI) No. 80,930/1991, Japanese Patent Publication (KOKAI) No. 145,017/1992, and Japanese Patent Publication (KOKAI) No. 25 159,218/1992. However, they all relate to gelatin capsules which contain a stabilizer in the gelatin coating and do not mention at all the adjustment of water activity inside the capsules. Therefore, these publications do not solve the above problems. Japanese Patent Publication (KOKAI) No. 24,014/1978 has reported gelatin capsules containing polyvinyl pyrrolidone. However, the amount of polyvinyl pyrrolidone used per capsule is only small and the purpose of its use is the adjustment of the release rate of a drug.

30 Under the above conditions, the present inventors have studied intensively to establish a method for adjusting the water activity inside a capsule (i.e., internal water activity of a capsule) appropriately, and to develop a capsule having adjusted water activity.

As a result, the present invention has been established on the basis of the finding that it is useful to add a certain substance which serves as a water activity regulating agent to the capsule content in order to adjust the internal water 35 activity of a capsule appropriately without affecting adversely the gelatin coating.

The present invention provides a gelatin capsule having adjusted water activity and preserved in a closed system, which contains, packed therein, an additive(s) selected from carboxymethyl cellulose calcium, crosscarmellose sodium, partially gelatinized starch and polyvinyl polypyrrolidone in the proportion of 50 to 150 wt. % of the total quantity of the gelatin of the said capsule.

40 In the drawings:

Fig. 1 is a graph showing the relation between temperature and water activity of gelatin which is preserved in a closed system.

45 Fig. 2 is a graph showing the stability of aspirin in a capsule which contains aspirin alone or in association with an additive (CS (cornstarch); MCC (crystalline cellulose); CMS (carboxymethyl cellulose Ca); PCS (partially gelatinized starch)), when preserved in a closed system while heated at 60°C.

Fig. 3 is a graph showing the relation between the addition ratio of an additive to gelatin and the water activity of gelatin beads in a mixture which contains gelatin beads and an additive (PVPP (polyvinyl polypyrrolidone); Ac-di-Sol; CMC-Ca; PCS) in various mixing ratios and preserved in a closed system (25°C).

50 Fig. 4 is a graph showing the relation between the addition ratio of an additive to gelatin and the water activity of gelatin beads in a mixture similar to that used in Fig. 3, which was preserved in a closed system while heated (45°C).

Fig. 5 is a graph showing the relation between the addition ratio of an additive to gelatin and the water activity of gelatin beads in a mixture similar to that used in Fig. 3, which was preserved in a closed system while heated 55 (60°C).

The coating of the gelatin capsules of the present invention preferably contains as a principal component gelatin and optionally a small amount of an additive(s) for capsule coating generally used in the field of pharmaceutical indus-

tries, for example, polyethylene glycol.

For the purposes of the present invention, a selected additive serving as a water activity regulating agent (or a regulator) as mentioned above is packed in a capsule in the proportion of about 50 to 150 wt. %, preferably about 50 to 120 wt. %, more preferably about 50 to 100 wt. %, further more preferably about 70 to 100 wt. %, especially preferably about 75 to 90 wt. % of the total quantity of the gelatin coating.

If the amount of the additive(s) is too small, the internal water activity cannot be controlled effectively when the capsule is preserved at high temperature and under high humidity, or for a long time, which can possibly lead to the destabilization or discoloration of the capsule or its content. If the amount of the additive(s) is too large, the internal water activity could be greatly decreased under the mild condition of room temperature and a crack may occur in the gelatin capsule.

Throughout the specification, the term "water activity ( $A_w$ )" means the ratio of water vapor pressure ( $P$ ) in a certain measurement system to that ( $P_0$ ) of pure water under the same temperature and pressure as those of the said measurement system, and is defined by the formula:

$$A_w = (P/P_0) \times 100 (\%)$$

The water activity of each gelatin, additive(s) and the whole capsule can be measured with any commercially available measuring device (e.g., the Water activity ( $A_w$ ) measurement system of the DT type, manufactured by Rotronic, Inc. (Gunze Industrial Co., Ltd.)).

The total water activity of a capsule ( $A_{WT}$ ) is in principle the same as the mean water activity ( $A_w$ ) which can be calculated from the water activity of each gelatin as a component of the capsule coating and the additive(s) packed in the capsule in accordance with the following formula. However, they differ from each other when a shift of moisture between coating and additives occurs due to the packing of an additive(s) into a capsule.

$$A_w = [A_w \cdot M(\text{gelatin}) + A_w \cdot M(\text{additive})] / [M(\text{gelatin}) + M(\text{additive})]$$

$A_w$ : mean water activity  
 $A_w$ : individual water activity  
 $M$ : individual water content

Throughout the specification, when "a change in water activity" is discussed in relation to the moisture stability of capsules, the difference between the mean water activity ( $A_w$ ) calculated according to the formula on the basis of the individual water activity before packing an additive(s) and the  $A_{WT}$  value of a capsule calculated after packing the additive(s) is more important than the change in the absolute water activity measured for each of the gelatin and the additive(s). That is, the greater the reduction of  $A_{WT}$  from  $A_w$  of a capsule, the more the water transferred from the capsule coating to the additive(s), which means that the elevation of water activity inside the said capsule is under suppression. The capsules of the present invention may contain any pharmacologically active and pharmaceutically acceptable drug, as long as it does not interact adversely with the additives. However, a substance which is liable to change in pharmacological activity and physicochemical characteristics such as color or particle size due to the change in water activity, especially an increase thereof, is suited. Examples of such substances include antibiotics, e.g., 7 $\beta$ -[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamide]-(1,2,3-triazol-4-ylthiomethylthio)-1-carba-3-cephem-4-carboxylic acid, and aspirin. Incidentally, in some cases, such a physicochemical change of a drug is attributable not only to the active substance but also the contaminants accompanying to the active substance.

The gelatin capsules obtained according to the present method are unexpectedly stable when preserved in a closed system, where gelatin capsules are usually unstable. Especially, a contained drug(s) which otherwise is adversely affected by high water activity can be kept stably in a gelatin capsule even in a closed system at elevated temperature. At the same time, the gelatin capsule coating itself has also been stabilized. Accordingly, the present invention can contribute to the maintenance of the quality of capsules which have previously been considered to be subject to quality deterioration during transportation or preservation.

Throughout the specification, the term "closed system" means a system where the distribution of outside air is blocked as completely as possible and is preferably constructed by packaging, for example with a press-through package (PTP) or alumi-pillow.

The capsules of the present invention can be prepared in a conventional manner using conventional carriers and excipients, except that an appropriate amount of additive(s) which serves as a water activity regulator is included. However, since an experiment revealed that additives such as cornstarch, crystalline cellulose, lactose, mannitol and sucrose, which are commonly formulated into standard capsules, affect adversely the water activity reduction (see Test Example 2 below), it is preferable to adjust the content of these additives adequately when they are used in the preparation of capsules of the present invention. For example, a relatively slight amount of such a substance, e.g., lactose, is

usable as an excipient when preparing the capsules of the present invention on condition that it does not affect adversely the reduction of water activity.

## EXAMPLES

The present invention will be described in more detail in the following Examples. However, these are merely for illustration purpose and should not be construed as limiting the scope of the present invention as claimed.

In the following Examples, water content and water activity of both the coating and the content of capsules were measured under the following conditions.

### Water activity:

Device: Water activity ( $A_w$ ) Measuring System of the DT type, manufactured by Rotronic & Co. (Gunze Industrial Co., Ltd.);

Specimen: 3 g; and

Temperature of jacket: 25+2°C; 45+2°C; or 60+2°C.

### Water content:

Thermostat: SATAKE Vacuuous Thermostat;

Temperature: 60+1°C;

Degree of vacuum: 5 mmHg or below (phosphorus pentoxide);

Desiccation time: 4 hours; and

Specimen: 0.5 - 1.0 g (container: diameter 1.7 cm, thickness of specimen: about 7 mm).

The measured values of water content were expressed by the proportion (%) of the weight loss (dry wt.) to the dry weight of the specimen.

### Test Example 1 Influence of Temperature on the Water activity of Gelatin

Water activity of gelatin to be used in the capsule coating was evaluated in a closed system under the conditions described above. The results obtained using gelatin alone are shown in Fig. 1.

From Fig. 1, it is apparent that the water activity of gelatin increases as temperature rises, i.e., 45% at 40°C; 55% at 50°C; and 70% at 60°C. These results indicate that, when heated under a sealed condition, moisture evaporates from the gelatin coating of a capsule, which in turn makes the condition of the inside of the capsule hyper humidity (hyper water activity).

### Test Example 2 Screening of Additives Showing Reduction of Water activity in the Presence of Gelatin

Screening of a substance suited for the reduction of water activity inside a gelatin capsule was conducted by preserving various additives alone or in a 1:1 mixture with gelatin (beads) in a closed system and determining the water activity and water content. Specifically, 1.5 g of an additive, or a mixture of 1.5 g of an additive and 1.5 of gelatin beads was placed in a vial, plugged to seal, and kept for 14 days at a constant temperature (25°C, 45°C or 60°C). The water activity and water content of the individual additive and gelatin were then measured. Water activity of the additive preserved in the presence of gelatin beads was measured with a device for measuring the water activity adjusted at the same temperature as storage. The water content of each additive following the preservation was measured under the conditions above after removing gelatin beads from the mixture. The results are shown in Table 1 below.

Table 1 (1)Water Activity

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	Additive (alone)			Additive + gelatin	
	(A <sub>v</sub> )			(A <sub>vt</sub> )	
	25°C	45°C	60°C	45°C	60°C
Lactose	38.6	31.6	32.3	57.0(57.8)	68.5(68.3)
Powdered					
Sugar	11.4	22.4	26.8	57.4(59.2)	67.8(70.4)
Mannitol	35.4	24.1	23.1	57.8(59.2)	67.2(70.2)
Cornstarch	41.2	61.2	73.4	67.4(60.2)	78.6(71.8)
Crystalline					
cellulose	36.9	54.2	63.3	56.1(58.0)	67.4(68.5)
L-HPLC	15.1	30.0	38.2	45.4(51.9)	56.3(62.2)
Gelatin					
(alone)	39.2	59.3	70.3	-	-
PVPP	6.1	20.0	26.6	34.3(49.0)	46.9(58.9)
Ac-Di-Sol	3.8	13.3	21.0	30.1(52.2)	41.1(62.7)
CMC-Ca	2.2	11.4	20.0	30.9(54.8)	42.6(60.2)
PCS	16.0	32.4	39.1	44.4(54.8)	56.8(65.1)

## Note:

the figure in ( ) shows the mean water activity  
(A<sub>w</sub>) calculated from the measurements on  
gelatin and individual additive.

**Table 1 (2)**Water Content

		Additive + gelatin		
		25°C	45°C	60°C
	Lactose	0.74	0.69	0.50
	Powdered Sugar	0.02	0.02	0.04
	Mannitol	0.04	0.05	0.05
	Cornstarch	12.06	11.93	11.44
	Crystalline			
	cellulose	4.36	4.31	4.31
	L-HPLC	4.38	5.69	5.86
	<u>Gelatin (alone)</u>	<u>13.0</u>	<u>-</u>	<u>-</u>
	PVPP	4.61	6.83	6.81
	Ac-Di-Sol	2.37	5.38	5.61
	CMC-Ca	3.26	6.24	6.68
	<u>PCS</u>	<u>2.58</u>	<u>7.95</u>	<u>8.04</u>

**Note:**

Preserving conditions: Sealed in a vial at 25°C,  
45°C or 60°C for 14 days (1.5 g gelatin + 1.5 g  
additive)

L-HPC: low-substituted-hydroxypropyl cellulose

PVPP: polyvinyl polypyrrolidone

Ac-Di-Sol (Asahi Kasei/FMC Corporation)

CMC-Ca: carboxymethyl cellulose calcium

PCS: partially gelatinized starch

Table 1 shows that polyvinyl polypyrrolidone (PVPP), crosscarmellose sodium (Ac-Di-Sol), carboxymethyl cellulose calcium (CMC-Ca), and partially gelatinized starch (PCS) are useful for the reduction of water activity inside a capsule.

Table 1 also shows that both the cornstarch and crystalline cellulose, which are often used in a standard formulation for capsules, function adversely to the reduction of water activity, which indicates that one must be careful when these additives are used in a formulation containing a drug(s) subject to influence of moisture.

Test Example 3 Stability of Aspirin in Capsules Preserved in a Closed System under Heating

The test was carried out by filling a powder mixture (160 mg) of aspirin (AS) and an additive (1:1) into a hard gelatin capsule (No. 4), keeping the capsule in a closed system set by the use of a BVK14 vial while heating at 60°C, and measuring the time-course of the aspirin content. The results are shown in Fig. 2.

From Fig. 2, it is clear that aspirin decomposes markedly when preserved alone. The decomposition of aspirin is, however, inhibited in the presence of partially gelatinized starch (PCS) or carboxymethyl cellulose calcium (CMC), but accelerated in the presence of cornstarch (CS) or crystalline cellulose (MCC).

# EP 0 818 195 A1

## Test Example 4 Chemical Stability of Aspirin Capsules Containing Additives in Various Ratios

Gelatin capsules containing aspirin (AS) as a model drug in the ratio of 1.5 to the gelatin were prepared in the absence or the presence of an additive (PVPP, Ac-Di-Sol, CMC-Ca, PCS) at various combination ratios ((r) = 0.2, 0.5, 1.0, 1.5) to the gelatin. The capsules were then subjected to an acceleration test (at 45°C for 3 months) corresponding to a normal time-course test (at room temperature for 2 years), or a severe test (at 60°C for 2 weeks), and the residual rate (%) of aspirin and the water activity (AWT) Of the capsule containing aspirin were measured. The results are shown in Table 2 below.

Table 2

	Wt.ratio	Residual rate(%)		Water activity(%)	
		45°C,	3 mon.	60°C,	2 weeks
AS / GEL-Cap	(1.5) / 1.0	84.1	(63.9)	77.2	(75.7)
AS + PVPP / GEL-Cap	(1.5, 0.2) / 1.0	93.3	(48.0)	83.6	(64.0)
	(1.5, 0.5) / 1.0	98.0	(42.0)	90.3	(56.2)
	(1.5, 1.0) / 1.0	99.8	(35.2)	92.8	(48.0)
	(1.5, 1.5) / 1.0	100.0	(31.2)	98.0	(44.0)
AS + Ac-Di-Sol / GEL-Cap	(1.5, 0.2) / 1.0	93.8	(46.4)	85.5	(60.9)
	(1.5, 0.5) / 1.0	100.0	(37.8)	90.2	(53.6)
	(1.5, 1.0) / 1.0	100.0	(30.6)	97.0	(43.2)
	(1.5, 1.5) / 1.0	100.0	(25.4)	99.9	(36.8)
AS + CMC-Ca / GEL-Cap	(1.5, 0.2) / 1.0	94.2	(46.5)	85.4	(62.1)
	(1.5, 0.5) / 1.0	100.0	(37.8)	92.1	(53.6)
	(1.5, 1.0) / 1.0	100.0	(32.0)	99.3	(44.5)
	(1.5, 1.5) / 1.0	100.0	(26.2)	100.0	(36.9)
AS + PCS / GEL-Cap	(1.5, 0.2) / 1.0	95.2	(49.1)	83.6	(66.8)
	(1.5, 0.5) / 1.0	100.0	(39.8)	92.8	(58.4)
	(1.5, 1.0) / 1.0	100.0	(39.8)	99.8	(52.2)
	(1.5, 1.5) / 1.0	100.0	(36.0)	100.0	(48.3)

Table 2 shows that, in the case of the acceleration test (45°C, 3 months), the aspirin content decreases to about 84% in the absence of an additive, while the decrease in the aspirin content could be almost suppressed by packing any one of four kinds of additives in the proportion of about 50 wt. % or more of the gelatin coating. Further, even in the case of the severe test at 60°C for 2 weeks, it is possible to secure the aspirin residual rate of 90% or more by packing an additive in a capsule in the proportion of about 50% or more of the gelatin coating.

## Test Example 5 Influence of Combination Ratio of Additive to Gelatin on Water Activity

An additive (PVPP, Ac-Di-Sol, CMC-Ca or PCS), which proved to be effective in the reduction of water activity in Test Example 2 above, was mixed with gelatin beads at a given combination ratio (r) to obtain a mixture containing 1.5 g of gelatin beads and (1.5 x (r)) g of an additive wherein (r) = 0, 0.2, 0.5, 1.0, 1.5. The resulting mixture was then subjected to the measurement of water activity in the same manner as described in Test Example 2 after preserving in a sealed vial for 14 days under heating (25°C, 45°C or 60°C). The results obtained after preserving at 25°C, 45°C and 60°C are provided in Figs. 3, 4 and 5, respectively. Figs. 3 - 5 show that the additives capable of reducing the water activity decrease the water activity of the system as a whole under any temperature condition depending on the amount used, and that the water activity of the system increases with the elevation of temperature irrespective of the kind of additive. In the figures, "a" indicates the water activity at which a crack(s) possibly occurs to the number 4 capsule coating, which contains 4.6% PEG (polyethylene glycol) (cap & body OP. white, Japan Eranco). When the water activity

## EP 0 818 195 A1

decreases below the value at "a", the plasticity of the capsule coating decreases, leading to an increase in the probability of occurrence of cracks due to breakage during transport or preservation. As is shown in Fig. 3, the preferred combination rate of an additive to capsule coating is 150 % or less, at the storage temperature of 25°C.

### 5 Example 1

Capsules were prepared from the following components.

10

Aspirin	112.4 mg
CMC-Ca	35.0 mg
Carplex 67 (Shionogi)	1.7 mg
Magnesium stearate	1.7 mg
	<u>150.8 mg</u>

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20 The above components were mixed and the powder mixture was filled into a hard gelatin capsule of size No. 4 (40 mg) to obtain a capsule (190.8 mg).

### Example 2

Capsules were prepared from the following components.

25

Aspirin	112.4 mg
CMC-Ca	30.0 mg
Carplex 67 (Shionogi)	1.5 mg
Magnesium stearate	1.5 mg
Lactose	9.6 mg
	<u>155.0 mg</u>

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The above components were mixed and the powder mixture was filled into a hard gelatin capsule of size No. 4 (40 mg) to obtain a capsule (190.5 mg).

### 40 Example 3

Capsules were prepared from the following components.

45

Aspirin	107.0 mg
Ac-Di-Sol	40.0 mg
Carplex 67 (Shionogi)	1.0 mg
Magnesium stearate	2.0 mg
Lactose	5.0 mg
	<u>155.0 mg</u>

50

55 The above components were mixed and the powder mixture was filled into a hard gelatin capsule of size No. 4 (40 mg) to obtain a capsule (190.5 mg).

**Example 4**

Capsules were prepared from the following components.

Aspirin	102.0 mg
PVPP	48.0 mg
Carplex 67 (Shionogi)	1.0 mg
Magnesium stearate	2.0 mg
Lactose	2.0 mg
	<hr/> 155.0 mg

The above components were mixed and the powder mixture was filled into a hard gelatin capsule of size No. 4 (40 mg) to obtain a capsule (190.5 mg).

As is apparent from the results shown in the Test Examples, the gelatin capsule of the invention maintains the water activity adequately even in a closed system under heating. Accordingly, the present invention provides a gelatin capsule which is not only stable but also able to keep its content comprising a drug(s) susceptible to the influence of moisture stably for a long time, and thereby contributing to the maintenance of the quality of the capsules.

**Claims**

1. A gelatin capsule having adjusted water activity and preserved in a closed system, which contains, packed herein, an additive(s) selected from the group consisting of carboxymethyl cellulose calcium, crosscarmellose sodium, partially gelatinized starch and polyvinyl polypyrrolidone in the proportion of 50 to 150 wt. % of the total quantity of the gelatin of the said capsule.
2. The gelatin capsule of claim 1 wherein the additive(s) is packed in the proportion of 50 to 120 wt. % of the total quantity of the gelatin.
3. The gelatin capsule of claim 1 or 2 wherein the additive is carboxymethyl cellulose calcium.
4. The gelatin capsule of any one of claims 1 to 3, which is packaged in a press-through package.
5. A method of stabilizing a gelatin capsule characterized in that an additive(s) selected from the group consisting of carboxymethyl cellulose calcium, crosscarmellose sodium, partially gelatinized starch and polyvinyl polypyrrolidone is used as a water activity regulating agent.

Fig. 1

Relation between temperature and water activity of gelatin

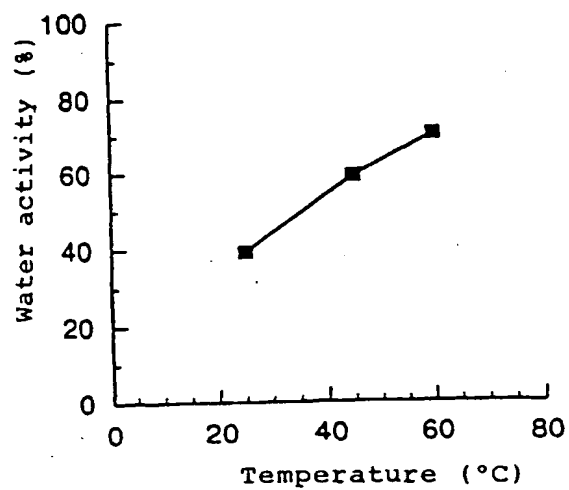
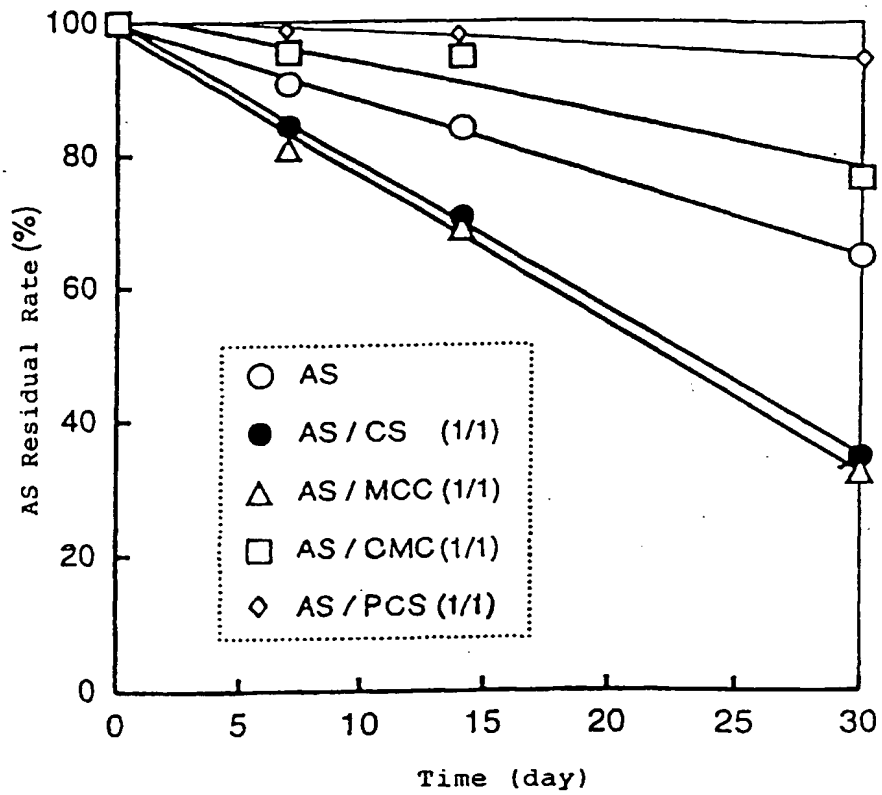


Fig. 2



( CS : Cornstarch  
MCC : Crystalline cellulose  
CMC : Carboxymethyl cellulose Ca  
PCS : Partially gelatinized starch )

Fig. 3

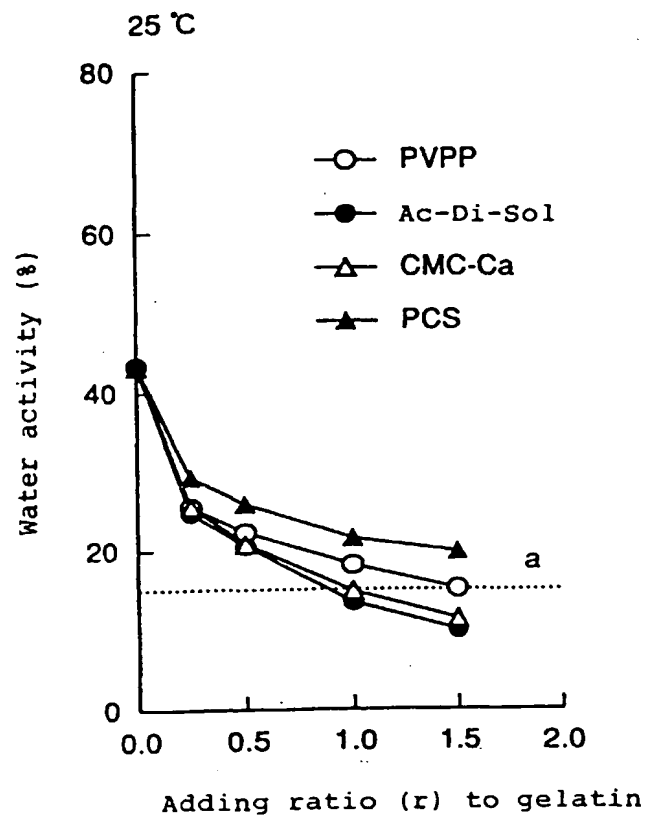


Fig. 4

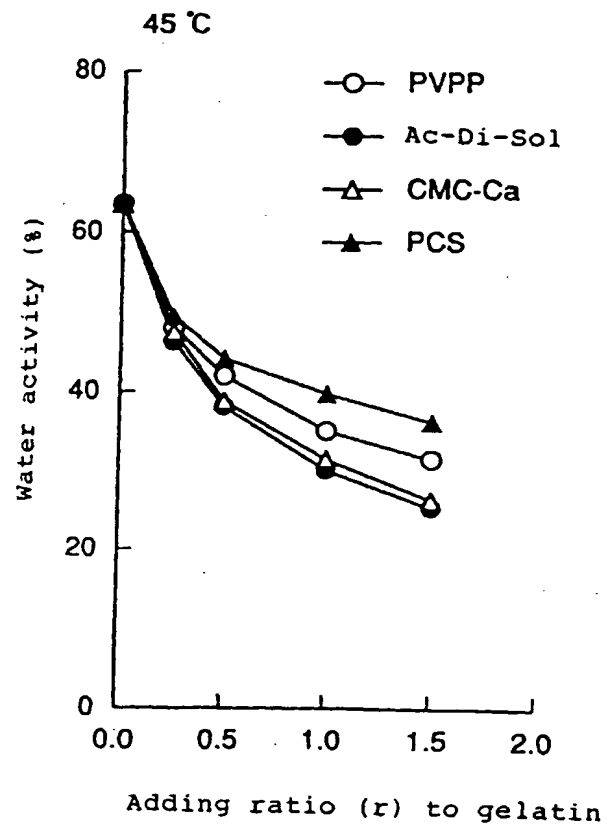
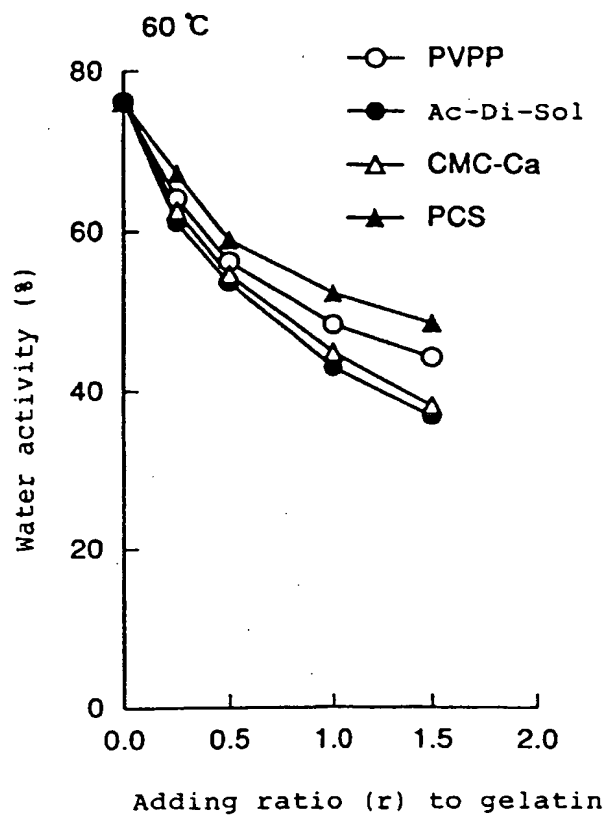


Fig. 5



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP96/00728

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int. C1 <sup>6</sup> A61K9/48, A61J3/07 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int. C1 <sup>6</sup> A61K9/48, A61J3/07 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 63-174929, A (Eran Corp. PLC), July 19, 1988 (19. 07. 88), Claim, example 5 & EP, 274176, A	1, 2
X	JP, 61-18725, A (Bayer AG.), January 27, 1986 (27. 01. 86), Claim, lines 17 to 19, upper left column, page 4 & EP, 167909, A & US, 5266581, A	1, 2
A	JP, 61-57522 (The Upjohn Co.), March 24, 1986 (24. 03. 86) & EP, 172014, A	1
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search June 11, 1996 (11. 06. 96)		Date of mailing of the international search report June 18, 1996 (18. 06. 96)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)